IGF-II and NSC-631570 compounds affect PMP22 gene expression in pancreatic ductal adenocarcinoma - could be the new target for both chemo-resistance and neuronal invasion

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Context: Peripheral myelin protein 22 gene (PMP22) encodes a membrane protein of myelin in the peripheral nervous system, and PMP22 duplication causes the Charcot-Marie-Tooth 1A (CMT1A) phenotype. PMP22 is also capable of delaying the transition from G0/G1 to S phase (Growth Arrest Specific Gene 3, GAS3). However, growth factors involved in PMP22 regulation, such as insulin-like growth factor-II (IGF-II), are up-regulated after radiation in fibroblast cells, and might influence chemoradiosensitivity. Since the compound NSC-631570 had a protective effect on human fibroblasts but not human tumor cells against ionizing radiation, and showed beneficial effects in phase II studies in metastatic and locally advanced PDAC patients.

Objective: The aim of this study was to evaluate the interaction between PMP22, IGF-II and NSC-631570 in PDAC primary cell cultures (PCCs).

Methods: DNA duplication of PMP22 gene was evaluated by PCR and specific digestion by the endonucleases EcoRI and NsiI in 13 PDAC tissues, 2 PCCs and PBMCs from 3 healthy subjects (used as negative controls in genetic tests for the CMT1A syndrome). PMP22 protein expression was evaluated in tissues and cells by Immunohistochemistry (IHC), using a quantitative scoring (e.g., 0 absent, 1 low, 2 intermediate and 3 high expressions). The PCCs were also exposed to IGF-II, NSC-631570, and their combination. Finally, expression of PMP22 was correlated with cell proliferation index.

Results: The PMP22 duplication was observed in 44% (7/16) of PDAC patients and in both PCCs. PDAC duplicated samples showed significantly higher score of PMP22 protein expression (p=0.0262). PMP22 protein was correlated with decreased cell growth, whereas 400 nM IGF-II reduced PMP22 expression and increased cell proliferation. Conversely, the addition of 1μM NSC-631570 increased PMP22 expression, and overcame IGF-II induced proliferation.

Conclusion: This is the first study reporting PMP22 duplication in PDAC specimens and cells. This duplication was correlated with PMP22 expression. PMP22 protein was inversely related to cell proliferation and its inhibition by IGF-II might explain chemoradioresistance caused by PDAC associated fibroblasts. However, NSC-631570 increased PMP22 expression and might synergize with anticancer treatments against PDAC.

Biography
Niccola Funel has received his first graduation in Bio-Molecular Science (2000) from Pisa University, Italy, where he acquired both PhD graduation in Experimental and Molecular Oncology (2006) and Specialization in Clinical Pathology (2008). Since 2002, he has been working in different projects focused on Pancreatic Ductal Adenocarcinoma (PDAC). In 2010, he became the PI of his project regarding new therapeutic strategies against PDAC. In 2011, he is the Council Member of Italian Society for Pancreas Study (AISP) for three years. He is also EPC Member (European Pancreatic Club) and PC Member (Pancreatic Club) since 2009. He has been awarded six times from AISP at the annual meeting as a Young Investigator.

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